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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02027874.3

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
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Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

6-substituted benzimidazoles

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6-Substituted benzimidazoles

Technical field

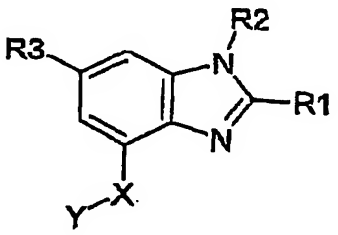
The invention relates to novel compounds, which are used in the pharmaceutical industry as active compounds for the production of medicaments.

Prior art

In European patent applications 266326 (which corresponds to US Patent 5,105,862), benzimidazole derivatives having a very broad variety of substituents are disclosed, which are said to be active as anti-ulcer agents.

Summary of the invention

The invention relates to compounds of the formula 1



(1)

In which

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy- 1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino1-4C-alkylcarbonyl, hydroxy-2-4C-alkyl, fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

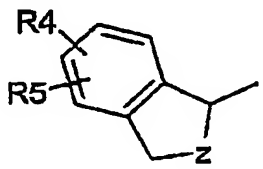
X is O (oxygen) or NH and

Y has either the meaning $-CH_2-Ar$

wherein

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,

or Y denotes the group gp



(gp)

wherein

Z has the meaning –CHR8- or –CHR8-CHR9-

where in Ar and/or in the group gp

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R6 is hydrogen, 1-4C-alkyl or halogen and

R7 is hydrogen, 1-4C-alkyl or halogen,

R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

with the proviso that R3 does not have the meaning hydrogen or halogen when Y denotes $-CH_2-Ar$,

and the salts of these compounds.

1-4C-Alkyl represents straight-chain or branched alkyl groups having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and the methyl group.

3-7C-Cycloalkyl represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkyl-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the aforementioned 3-7C-cycloalkyl groups. Examples which may be mentioned are the cyclopropylmethyl, the cyclohexylmethyl and the cyclohexylethyl group.

1-4C-Alkoxy represents groups, which in addition to the oxygen atom contain a straight-chain or branched alkyl group having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy group.

1-4C-Alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one of the aforementioned 1-4C-alkoxy groups. Examples which may be mentioned are the methoxymethyl, the methoxyethyl group and the butoxyethyl group.

1-4C-Alkoxycarbonyl (-CO-1-4C-alkoxy) represents a carbonyl group, to which one of the aforementioned 1-4C-alkoxy groups is bonded. Examples which may be mentioned are the methoxycarbonyl (CH_3O-C(O)-) and the ethoxycarbonyl group (CH_3CH_2O-C(O)-) .

2-4C-Alkenyl represents straight-chain or branched alkenyl groups having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butenyl, 3-butenyl, 1-propenyl and the 2-propenyl group (allyl group).

2-4C-Alkynyl represents straight-chain or branched alkynyl groups having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butynyl, 3-butynyl, and preferably the 2-propynyl, group (propargyl group).

Fluoro-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by one or more fluorine atoms. An example which may be mentioned is the trifluoromethyl group.

Hydroxy-1-4C-alkyl represents aforementioned 1-4C-alkyl groups, which are substituted by a hydroxy group. Examples which may be mentioned are the hydroxymethyl, the 2-hydroxyethyl and the 3-hydroxypropyl group.

Mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyl represents a 1-4C-alkylcarbonyl group, which is substituted by a mono- or di-1-4C-alkylamino groups. Examples, which may be mentioned, are the dimethylamino-methylcarbonyl and the dimethylamino-ethylcarbonyl group.

Fluoro-2-4C-alkyl represents a 2-4C-alkyl groups, which is substituted by one or more fluorine atoms. An example which may be mentioned is the 2,2,2-trifluoroethyl group.

Halogen within the meaning of the invention is bromo, chloro and fluoro.

1-4C-Alkoxy-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by a further 1-4C-alkoxy group. Examples which may be mentioned are the groups 2-(methoxy)ethoxy (CH_3-O-CH_2-CH_2-O-) and 2-(ethoxy)ethoxy (CH_3-CH_2-O-CH_2-CH_2-O-).

1-4C-Alkoxy-1-4C-alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkoxy-1-4C-alkyl groups, which is substituted by one of the aforementioned 1-4C-alkoxy groups. An example which may be mentioned is the group 2-(methoxy)ethoxymethyl (CH_3-O-CH_2-CH_2-O-CH_2-).

Fluoro-1-4C-alkoxy-1-4C-alkyl represents one of the aforementioned 1-4C-alkyl groups, which is substituted by a fluoro-1-4C-alkoxy group. Fluoro-1-4C-alkoxy in this case represents one of the aforementioned 1-4C-alkoxy groups, which is completely or mainly substituted by fluorine. Examples of completely or mainly fluoro-substituted 1-4C-alkoxy groups which may be mentioned are the 1,1,1,3,3,3-hexafluoro-2-propoxy, the 2-trifluoromethyl-2-propoxy, the 1,1,1-trifluoro-2-propoxy, the perfluoro-tert-butoxy, the 2,2,3,3,4,4,4-heptafluoro-1-butoxy, the 4,4,4-trifluoro-1-butoxy, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy group.

1-7C-Alkyl represents straight-chain or branched alkyl groups having 1 to 7 carbon atoms. Examples which may be mentioned are the heptyl, isoheptyl (5-methylhexyl), hexyl, isohexyl (4-methylpentyl), neohexyl (3,3-dimethylbutyl), pentyl, isopentyl (3-methylbutyl), neopentyl (2,2-dimethylpropyl), butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and the methyl group.

2-7C-Alkenyl represents straight-chain or branched alkenyl groups having 2 to 7 carbon atoms. Examples which may be mentioned are the 2-butenyl, 3-butenyl, 1-propenyl, the 2-propenyl (allyl) and the vinyl group. The aforementioned 2-4C-alkenyl groups are preferred.

Oxo-substituted 1-4C-alkoxy represents a 1-4C-alkoxy group, which instead of a methylene group contains a carbonyl group. An example which may be mentioned is the 2-oxopropoxy group.

3-7C-Cycloalkoxy represents cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkyl-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by one of the aforementioned 3-7C-cycloalkyl groups. Examples which may be mentioned are the cyclopropylmethoxy, the cyclobutylmethoxy and the cyclohexylethoxy group.

Hydroxy-1-4C-alkoxy represents aforementioned 1-4C-alkoxy groups, which are substituted by a hydroxy group. A preferred example which may be mentioned is the 2-hydroxyethoxy group.

1-4C-Alkoxy-1-4C-alkoxy-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by one of the aforementioned 1-4C-alkoxy-1-4C-alkoxy groups. A preferred example which may be mentioned is the methoxyethoxyethoxy group.

3-7C-Cycloalkoxy-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by one of the aforementioned 3-7C-cycloalkoxy groups. Examples which may be mentioned are the cyclopropoxymethoxy, the cyclobutoxymethoxy and the cyclohexyloxyethoxy group.

3-7C-Cycloalkyl-1-4C-alkoxy-1-4C-alkoxy represents one of the aforementioned 1-4C-alkoxy groups, which is substituted by one of the aforementioned 3-7C-cycloalkyl-1-4C-alkoxy groups. Examples which may be mentioned are the cyclopropylmethoxyethoxy, the cyclobutylmethoxyethoxy and the cyclohexylethoxyethoxy group.

1-4C-Alkylcarbonyl represents a group, which in addition to the carbonyl group contains one of the aforementioned 1-4C-alkyl groups. An example which may be mentioned is the acetyl group.

1-4C-Alkylcarbonyloxy represents a 1-4C-alkylcarbonyl group which is bonded to an oxygen atom. An example which may be mentioned is the acetoxy group (CH_3CO-O-).

Halo-1-4C-alkoxy represents 1-4C-alkoxy groups which are completely or mainly substituted by halogen. "Mainly" in this connection means that more than half of the hydrogen atoms in the 1-4C-alkoxy groups are replaced by halogen atoms. Halo-1-4C-alkoxy groups are primarily chloro- and/or in particular fluoro-substituted 1-4C-alkoxy groups. Examples of halogen-substituted 1-4C-alkoxy groups which may be mentioned are the 2,2,2-trichloroethoxy, the hexachloroisopropoxy, the pentachloroisopropoxy, the 1,1,1-trichloro-3,3,3-trifluoro-2-propoxy, the 1,1,1-trichloro-2-methyl-2-propoxy, the 1,1,1-trichloro-2-propoxy, the 3-bromo-1,1,1-trifluoro-2-propoxy, the 3-bromo-1,1,1-trifluoro-2-butoxy, the 4-bromo-3,3,4,4-tetrafluoro-1-butoxy, the chlorodifluoromethoxy, the 1,1,1,3,3,3-hexafluoro-2-propoxy, the 2-trifluoromethyl-2-propoxy, the 1,1,1-trifluoro-2-propoxy, the perfluoro-tert-butoxy, the 2,2,3,3,4,4,4-heptafluoro-1-butoxy, the 4,4,4-trifluoro-1-butoxy, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy group.

Mono- or di-1-4C-alkylamino represents an amino group, which is substituted by one or by two - identical or different - groups from the aforementioned 1-4C-alkyl groups. Examples which may be mentioned are the dimethylamino, the diethylamino and the diisopropylamino group.

1-4C-Alkylcarbonyl represents a group, which in addition to the carbonyl group contains one of the aforementioned 1-4C-alkyl groups. An example which may be mentioned is the acetyl group.

1-4C-Alkylcarbonylamino represents an amino group to which a 1-4C-alkylcarbonyl group is bonded. Examples which may be mentioned are the propionylamino ($C_3H_7C(O)NH$-) and the acetylamino group (acetamido group) ($CH_3C(O)NH$-) .

1-4C-Alkoxycarbonylamino represents an amino group, which is substituted by one of the aforementioned 1-4C-alkoxycarbonyl groups. Examples, which may be mentioned, are the ethoxycarbonylamino and the methoxycarbonylamino group.

Mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy represents a 1-4C-alkylcarbonyloxy group, which is substituted by one of the aforementioned mono- or di-1-4C-alkylamino groups. Examples, which may be mentioned, are the dimethylamino-methylcarbonyloxy and the dimethylamino-ethylcarbonyloxy group.

1-4C-Alkoxy-1-4C-alkoxycarbonyl represents a carbonyl group, to which one of the aforementioned 1-4C-alkoxy-1-4C-alkoxy groups is bonded. Examples which may be mentioned are the 2-(methoxy)-ethoxycarbonyl (CH_3-O-CH_2CH_2-O-CO-) and the 2-(ethoxy)ethoxycarbonyl group (CH_3CH_2-O-CH_2CH_2-O-CO-).

1-4C-Alkoxy-1-4C-alkoxycarbonylamino represents an amino group, which is substituted by one of the aforementioned 1-4C-alkoxy-1-4C-alkoxycarbonyl groups. Examples which may be mentioned are the 2-(methoxy)ethoxycarbonylamino and the 2-(ethoxy)ethoxycarbonylamino group.

2-4C-Alkenyloxy represents groups, which in addition to the oxygen atom contain one of the abovementioned 2-4C-alkenyl groups. Examples, which may be mentioned, are the 2-butenyloxy, 3-butenyloxy, 1-propenyloxy and the 2-propenyloxy group (allyloxy group).

Carboxy-1-4C-alkyl represents 1-4C-alkyl groups which are substituted by a carboxyl group. Examples, which may be mentioned, are the carboxymethyl and the 2-carboxyethyl group.

1-4C-Alkoxycarbonyl-1-4C-alkyl represents 1-4C-alkyl groups, which are substituted by one of the abovementioned 1-4C-alkoxycarbonyl groups. Examples, which may be mentioned, are the Methoxy-carbonylmethyl and the ethoxycarbonylmethyl group.

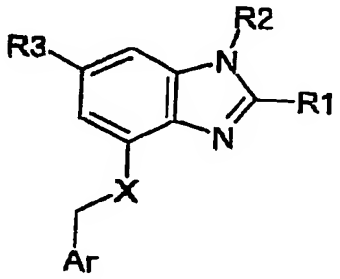
Possible salts of compounds of the formula 1 or 2 - depending on substitution - are especially all acid addition salts. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-

hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, where the acids are used in salt preparation - depending on whether a mono- or polybasic acid is concerned and on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can initially be obtained, for example, as process products in the production of the compounds according to the invention on the industrial scale, are converted into the pharmacologically tolerable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to invention and their salts, if, for example, they are isolated in crystalline form, can contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula I, and also all solvates and in particular all hydrates of the salts of the compounds of the formula I.

In one aspect, the invention relates to compounds of the formula 1a



(1a)

in which

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy- 1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino1-4C-alkylcarbonyl, hydroxy-2-4C-alkyl, fluoro-2-4C-alkyl,

R3 is fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32, where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

X is O (oxygen) or NH and

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, ben-

benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,

where

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R6 is hydrogen, 1-4C-alkyl or halogen and

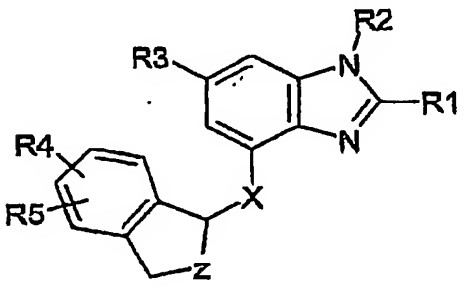
R7 is hydrogen, 1-4C-alkyl or halogen,

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

and the salts of these compounds.

In another aspect of the invention relates to compounds of the formula 1b



(1b)

in which

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy- 1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino1-4C-alkylcarbonyl, hydroxy-2-4C-alkyl, fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

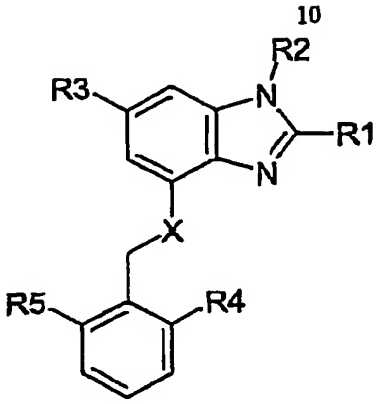
X is O (oxygen) or NH and

Z has the meaning –CHR8- or –CHR8-CHR9-
where
R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,
R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,
and wherein
aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

and the salts of these compounds.

The compounds of the formula 1b have up to three chiral centers in the parent structure. The invention thus relates to all conceivable stereoisomers in any desired mixing ratio to one another, including the pure enantiomers, which are a preferred subject of the invention.

Among the compounds of the formula 1a, preferred compounds are those of the formula 1a-1



(1a-1)

where

R1 is hydrogen or 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, or the group -CO-NR31R32,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

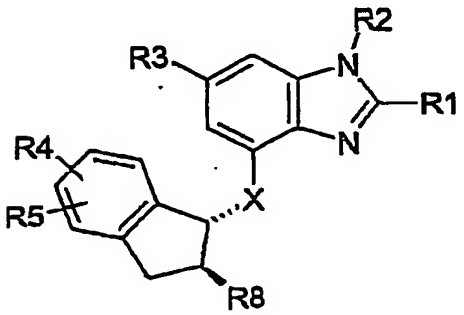
R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, trifluoromethyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

R5 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy and

X is O (oxygen) or NH,

and the salts of these compounds.

Among the compounds of the formula 1b, compounds of the formula 1b-1



(1b-1)

are preferred.

Preferred exemplary compounds of the formula 1b-1 are those, in which

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, -CO-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy or halogen,

R5 is hydrogen,

R8 is hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

X is O (oxygen) or NH,

and their salts.

Preferred compounds are those of formula 1a-1.

Particularly preferred compounds of the formula 1a-1 are those, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is carboxyl, -CO-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen or 1-4C-alkyl,

R4 is 1-4C-alkyl or 1-4C-alkylcarbonylamino,

R5 is 1-4C-alkyl,

X is O (oxygen) or NH,

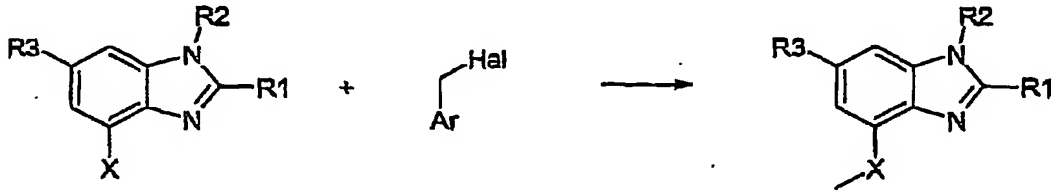
and their salts.

Particularly preferred are the compounds given as final products of formula 1 in the examples, and the salts of these compounds.

The compounds according to the invention can be synthesised from corresponding starting compounds, for example according to the reaction schemes given below. The synthesis is carried out in a manner known to the expert, for example as described in more detail in the following examples.

The starting compounds are known, for example from M. W. Lovell, S. G. Schulman, *Anal. Chem.* **1983**, *55*, 963-965 (e. g. 4-bromo-6-nitro-1,2-phenylenediamine). 6-Halo,4-nitro-substituted benzimidazoles are known in literature, for example 6-chloro-2-methyl-4-nitro-1(3)*H*-benzimidazole (Gillespie et al., *J. Org. Chem.* **1960**, *25*, 942) or they can be prepared using analogous process steps. 1,2-Epoxyindan is described for example in W. F. Whitmore; A. I. Gebhart, *J. Am. Chem. Soc.* **1942**, *64*, 912. In general, substituted alkyl-, alkoxy- or halogeno-epoxyindanes can be prepared from the corresponding substituted indenes by methods known from literature (e.g. epoxidation). The compounds of the general formula 1a can be obtained by reacting substituted benzimidazoles of formula I with compounds of formula II as depicted in scheme 1.

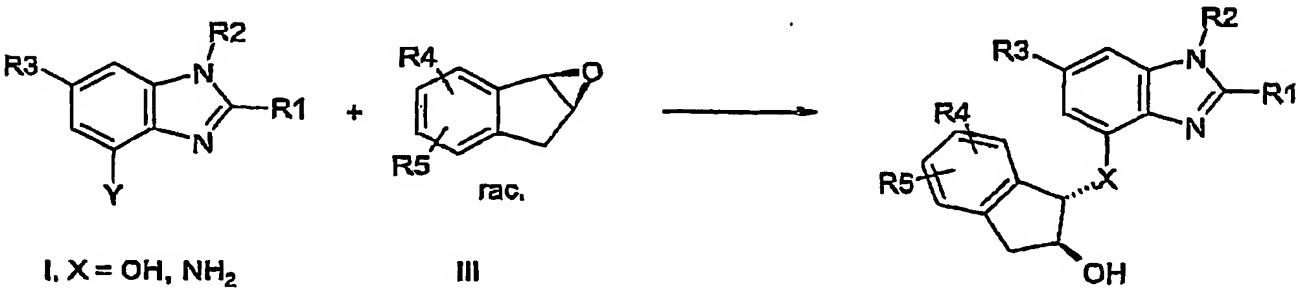
Scheme 1:



I, X = OH, NH_2 II 1a, X = O, NH

Analogously, compounds of the general formula 1b are obtained by reacting substituted benzimidazoles of formula I with epoxyindanes III, carrying any desired substituent R4 and R5 (cf. scheme 2 for a compound 1b-1).

Scheme 2:



I, X = OH, NH_2 III 1b-1, X = O, NH

The reaction steps outlined above are carried out in a manner known per se, e. g. as described in more detail in the examples. The derivatization, if any, of the compounds obtained according to the above

Scheme 1 and 2 (e.g. conversion of a group R3 into another group R3, or of R2 = H into another group R2, or conversion of the hydroxyl group into an alkoxy or ester group) is likewise carried out in a manner known per se. If compounds where R3 = -CO-1-4Calkoxy or R3 = -CO-NR31R32 are desired, an appropriate derivatization can be performed in a manner known per se (e. g. metal catalysed carbonylation of the corresponding bromo compound or conversion of an ester into an amide) at the stage of the benzimidazoles of formula I (scheme 1 and 2) or more conveniently at a later point in time.

The following examples serve to illustrate the invention in greater detail without restricting it. Likewise, further compounds of the formula 1 or 2 whose preparation is not described explicitly can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques. The abbreviation min stands for minute(s), h for hour(s).

Examples

1. 6-Bromo-2-methyl-4-nitro-1(3)*H*-benzimidazole

2.0 g (8.6 mmol) of 4-bromo-6-nitro-1,2-phenylenediamine are suspended in 18 ml of acetic anhydride and heated to 90 °C for 30 min. The reaction mixture is cooled in an ice bath and 60 ml of 5N hydrochloric acid are carefully added. After complete addition, the reaction mixture is refluxed for 1 h and poured onto crushed ice. The pH is adjusted to 8 by the addition of 6N aqueous potassium hydroxide solution. The mixture is extracted with ethyl acetate, the organic phase is dried over anhydrous magnesium sulfate and evaporated. Crystallization from diethyl ether/light petroleum ether yields 1.6 g (73 %) of the title compound as a yellow solid (m.p. 227-228 °C).

2. 6-Bromo-1,2-dimethyl-4-nitro-1*H*-benzimidazole

To a solution of 1.3 g (5.1 mmol) of 6-bromo-2-methyl-4-nitro-1(3)*H*-benzimidazole in 60 ml of N,N-dimethylformamide are added 0.3 g (7.6 mmol) of sodium hydride (60 % *w/w* dispersion in mineral oil) in portions at 0 °C. After 30 min, a solution of 0.47 ml (7.6 mmol) of methyliodide in 5 ml of N,N-dimethylformamide is slowly added and the reaction mixture is stirred for 30 min at 0 °C. After 1 h at room temperature, the reaction mixture is poured onto crushed ice. The mixture is extracted with ethyl acetate, the organic phase is dried over anhydrous magnesium sulfate and evaporated. Crystallization from ethyl acetate/n-heptane yields 0.41 g (30 %) of the title compound as a colourless solid (m.p. 175-178 °C).

3. 4-Amino-6-bromo-1,2-dimethyl-1*H*-benzimidazole

To a solution of 13.3 g (49.2 mmol) of 6-bromo-1,2-dimethyl-4-nitro-1*H*-benzimidazole in 310 ml of methanol are added 8.0 g (49.2 mmol) of iron(III) chloride and 6.8 g of activated charcoal. The reaction mixture is heated to 80 °C and 12 ml of hydrazine hydrate (95 %) are slowly added. After refluxing for 4 h, the mixture is filtered and the precipitate washed with methanol. The filtrate is evaporated and the residue crystallized by treatment with diethyl ether to give 8.5 g (72 %) of the title compound as a solid (m.p. 205-207 °C).

4. 6-Bromo-4-(2-ethyl-6-methyl-benzylamino)-1,2-dimethyl-1*H*-benzimidazole

To a solution of 8.5 g (35.4 mmol) of 4-amino-6-bromo-1,2-dimethyl-1*H*-benzimidazole and 6.3 g (37.2 mmol) of 2-ethyl-6-methyl-benzylchloride in 425 ml of acetone are added 4.0 g (37.7 mmol) of sodium carbonate and 3.2 g (21.4 mmol) of sodium iodide. The reaction mixture is stirred for 20 h at room temperature and evaporated to 1/8 of its volume. After the addition of saturated aqueous ammonium chlo-

ride solution, the mixture is extracted with ethyl acetate, the organic phase is dried over anhydrous magnesium sulfate and evaporated. Purification of the residue by column chromatography on silica gel using ethyl acetate:light petroleum ether (4:6, *v/v*) yields 6.0 g (46 %) of the title compound as a colourless solid (m.p. 215-217 °C).

5. Ethyl 4-(2-ethyl-6-methyl-benzylamino)-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate

1.0 g (2.7 mmol) of 6-Bromo-4-(2-ethyl-6-methyl-benzylamino)-1,2-dimethyl-1*H*-benzimidazole are dissolved in 15 ml of absolute ethanol and 2.5 ml of triethylamine and transferred to an autoclave. After the addition of 0.1 g (0.45 mmol) of palladium(II) acetate and 0.33 g (1.25 mmol) of triphenylphosphine, the reaction mixture is carbonylated (5 bar carbon monoxide pressure, 100 °C) for 16 h. The reaction mixture is cooled down, filtered and evaporated to leave an orange coloured oil which is dissolved in ethyl acetate and extracted with water. The organic phase is dried over anhydrous magnesium sulfate and evaporated. Purification of the residue by crystallization from ethyl acetate/light petroleum ether yields 0.8 g (81 %) of the title compound as a colourless solid (m.p. 171-173 °C).

6. 4-(2-Ethyl-6-methyl-benzylamino)-1,2-dimethyl-1*H*-benzimidazole-6-carboxylic acid

To a solution of 5.0 g (13.7 mmol) of ethyl 4-(2-ethyl-6-methyl-benzylamino)-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate in 80 ml of dioxane are added 50 ml of 2N aqueous sodium hydroxide solution. After 1 h at reflux, the reaction mixture is evaporated to half of its volume and the pH is adjusted to 6 by the addition of 6N hydrochloric acid. The thick precipitate is collected, washed with water and dried *in vacuo* over phosphorus pentoxide. Filtration of the crude product over silica gel using dichloromethane:methanol (13:1, *v/v*) as eluent yields 3.0 g (65 %) of the title compound as a colourless solid (m.p. 280-282 °C).

7. 4-(2-Ethyl-6-methyl-benzylamino)-6-(2-hydroxyethylaminocarbonyl)-1,2-dimethyl-1*H*-benzimidazole

A suspension of 1.0 g (2.74 mmol) of ethyl 4-(2-ethyl-6-methyl-benzylamino)-1,2-dimethyl-1*H*-benzimidazole-6-carboxylate in 10 ml of 2-aminoethanol is heated to 110 °C for 30 h. The reaction mixture is cooled down, diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic phase is dried over anhydrous magnesium sulfate and evaporated. Purification of the residue by crystallization from ethyl acetate/diethyl ether yields 0.72 g (69 %) of the title compound as a colourless solid (m.p. 200-201 °C).

8. 6-(N,N-Dimethylaminocarbonyl)-4-(2-ethyl-6-methyl-benzylamino)-1,2-dimethyl-1*H*-benzimidazole

1.0 g (2.96 mmol) of 4-(2-ethyl-6-methyl-benzylamino)-1,2-dimethyl-1*H*-benzimidazole-6-carboxylic acid and 1.1 g (3.43 mmol) of O-(1*H*-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) are suspended in 50 ml of dichloromethane and 0.58 ml (3.25 mmol) of dimethylamine (5.6 M in ethanol) are added to the reaction mixture. After stirring for 3 h at room temperature 2 ml of methanol are added and the reaction mixture is extracted with water, the organic phase is separated, dried over anhydrous magnesium sulfate and evaporated. Purification of the residue by column chromatography on silica gel using dichloromethane:methanol (50:1, *v/v*) yields 0.2 g (18 %) of the title compound as a colourless solid (m.p. 120-122 °C).

9. 4-(2-Ethyl-6-methyl-benzylamino)-1,2-dimethyl-1*H*-benzimidazole-6-carboxamide

1.0 g (2.96 mmol) of 4-(2-ethyl-6-methyl-benzylamino)-1,2-dimethyl-1*H*-benzimidazole-6-carboxylic acid and 1.1 g (3.43 mmol) of O-(1*H*-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) are suspended in 50 ml of dichloromethane and ammonia gas is passed through the flask for 2 h. The reaction mixture is poured into 200 ml of saturated ammonium chloride solution and the pH is adjusted to 7 by the addition of 6N hydrochloric acid. The mixture is extracted with ethyl acetate, the organic phase is separated, dried over anhydrous magnesium sulfate and evaporated. Purification of the residue by column chromatography on silica gel using dichloromethane:methanol (95:5, *v/v*) and crystallization from diethyl ether yields 0.16 g (16 %) of the title compound as a colourless solid (m.p. 240-241 °C).

Commercial utility

The compounds of the formula 1 and 2 and their salts have valuable pharmacological properties which make them commercially utilizable. In particular, they exhibit marked inhibition of gastric acid secretion and an excellent gastric and intestinal protective action in warm-blooded animals, in particular humans. In this connection, the compounds according to the invention are distinguished by a high selectivity of action, an advantageous duration of action, a particularly good enteral activity, the absence of significant side effects and a large therapeutic range.

"Gastric and intestinal protection" in this connection is understood as meaning the prevention and treatment of gastrointestinal diseases, in particular of gastrointestinal inflammatory diseases and lesions (such as, for example, gastric ulcer, duodenal ulcer, gastritis, hyperacidic or medicament-related functional dyspepsia), which can be caused, for example, by microorganisms (e.g. Helicobacter pylori), bacterial toxins, medicaments (e.g. certain antiinflammatories and antirheumatics), chemicals (e.g. ethanol), gastric acid or stress situations.

In their excellent properties, the compounds according to the invention surprisingly prove to be clearly superior to the compounds known from the prior art in various models in which the antiulcerogenic and the antisecretory properties are determined. On account of these properties, the compounds of the formula 1 and 2 and their pharmacologically acceptable salts are outstandingly suitable for use in human and veterinary medicine, where they are used, in particular, for the treatment and/or prophylaxis of disorders of the stomach and/or intestine.

A further subject of the invention are therefore the compounds according to the invention for use in the treatment and/or prophylaxis of the abovementioned diseases.

The invention likewise includes the use of the compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the abovementioned diseases.

The invention furthermore includes the use of the compounds according to the invention for the treatment and/or prophylaxis of the abovementioned diseases.

A further subject of the invention are medicaments which comprise one or more compounds of the formula 1 or 2 and/or their pharmacologically acceptable salts.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the pharmacologically active compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries or excipients in the form of tablets, coated tablets, capsules, suppositories, patches (e.g. as TTS), emulsions, suspensions or solutions, the active compound content advantageously being between 0.1 and 95% and it being possible to obtain a pharmaceutical administration form exactly

adapted to the active compound and/or to the desired onset and/or duration of action (e.g. a sustained-release form or an enteric form) by means of the appropriate selection of the auxiliaries and excipients.

The auxiliaries and excipients which are suitable for the desired pharmaceutical formulations are known to the person skilled in the art on the basis of his/her expert knowledge. In addition to solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound excipients, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or, in particular, permeation promoters and complexing agents (e.g. cyclodextrins).

The active compounds can be administered orally, parenterally or percutaneously.

In general, it has proven advantageous in human medicine to administer the active compound(s) in the case of oral administration in a daily dose of approximately 0.01 to approximately 20, preferably 0.05 to 5, in particular 0.1 to 1.5, mg/kg of body weight, if appropriate in the form of several, preferably 1 to 4, individual doses to achieve the desired result. In the case of a parenteral treatment, similar or (in particular in the case of the intravenous administration of the active compounds), as a rule, lower doses can be used. The establishment of the optimal dose and manner of administration of the active compounds necessary in each case can easily be carried out by any person skilled in the art on the basis of his/her expert knowledge.

If the compounds according to the invention and/or their salts are to be used for the treatment of the abovementioned diseases, the pharmaceutical preparations can also contain one or more pharmacologically active constituents of other groups of medicaments, for example: tranquillizers (for example from the group of the benzodiazepines, for example diazepam), spasmolytics (for example, bietamiverine or camylofine), anticholinergics (for example, oxyphencyclimine or phencarbamide), local anesthetics, (for example, tetracaine or procaine), and, if appropriate, also enzymes, vitamins or amino acids.

To be emphasized in this connection is in particular the combination of the compounds according to the invention with pharmaceuticals which inhibit acid secretion, such as, for example, H_2 blockers (e.g. cimetidine, ranitidine), H^+/K^+ ATPase inhibitors (e.g. omeprazole, pantoprazole), or further with so-called peripheral anticholinergics (e.g. pirenzepine, telenzepine) and with gastrin antagonists with the aim of increasing the principal action in an additive or super-additive sense and/or of eliminating or of decreasing the side effects, or further the combination with antibacterially active substances (such as, for example, cephalosporins, tetracyclines, penicillins, macrolides, nitroimidazoles or alternatively bismuth salts) for the control of Helicobacter pylori. Suitable antibacterial co-components which may be mentioned are, for example, mezlocillin, ampicillin, amoxicillin, cefalothin, cefoxitin, cefotaxime, imipenem, gentamycin, amikacin, erythromycin, ciprofloxacin, metronidazole, clarithromycin, azithromycin and combinations thereof (for example clarithromycin + metronidazole).

In view of their excellent gastric and intestinal protection action, the compounds of formula 1 are suited for a free or fixed combination with those medicaments (e.g. certain antiinflammatories and antirheumatics, such as NSAIDs), which are known to have a certain ulcerogenic potence.

Pharmacology

The excellent gastric protective action and the gastric acid secretion-inhibiting action of the compounds according to the invention can be demonstrated in investigations on animal experimental models. The compounds according to the invention investigated in the model mentioned below have been provided with numbers which correspond to the numbers of these compounds in the examples.

Testing of the secretion-inhibiting action on the perfused rat stomach

In Table A which follows, the influence of the compounds according to the invention on the pentagastrin-stimulated acid secretion of the perfused rat stomach after intraduodenal administration in vivo is shown.

Table A

No.	Dose (µmol/kg) i.d.	Inhibition of acid secretion (%)
7	1	56
8	1	100
9	1	100

Methodology

The abdomen of anesthetized rats (CD rat, female, 200-250 g; 1.5 g/kg i.m. urethane) was opened after tracheotomy by a median upper abdominal incision and a PVC catheter was fixed transorally in the esophagus and another via the pylorus such that the ends of the tubes just projected into the gastric lumen. The catheter leading from the pylorus led outward into the right abdominal wall through a side opening.

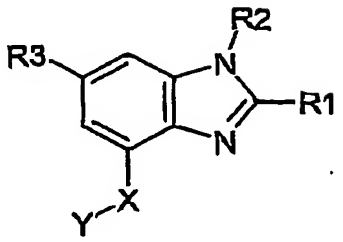
After thorough rinsing (about 50-100 ml), warm (37°C) physiological NaCl solution was continuously passed through the stomach (0.5 ml/min, pH 6.8-6.9; Braun-Unita I). The pH (pH meter 632, glass electrode EA 147; ϕ = 5 mm, Metrohm) and, by titration with a freshly prepared 0.01N NaOH solution to pH 7 (Dosimat 665 Metrohm), the secreted HCl were determined in the effluent in each case collected at an interval of 15 minutes.

The gastric secretion was stimulated by continuous infusion of 1 µg/kg (= 1.65 ml/h) of i.v. pentagastrin (left femoral vein) about 30 min after the end of the operation (i.e. after determination of 2 preliminary fractions). The substances to be tested were administered intraduodenally in a 2.5 ml/kg liquid volume 60 min after the start of the continuous pentagastrin infusion.

The body temperature of the animals was kept at a constant 37.8-38°C by infrared irradiation and heat pads (automatic, stepless control by means of a rectal temperature sensor).

Patent claims

1. A compound of the formula 1



(1)

in which

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy- 1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino1-4C-alkylcarbonyl, hydroxy-2-4C-alkyl, fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,

where

R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

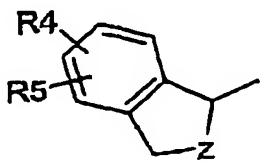
X is O (oxygen) or NH and

Y has either the meaning $-CH_2-Ar$

wherein

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,

or Y denotes the group gp



(gp)

wherein

Z has the meaning –CHR8- or –CHR8-CHR9-

where in Ar and/or in the group gp

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

R6 is hydrogen, 1-4C-alkyl or halogen and

R7 is hydrogen, 1-4C-alkyl or halogen,

R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

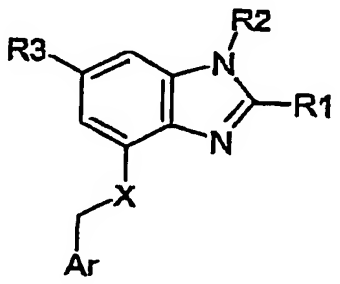
and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

with the proviso that R3 does not have the meaning hydrogen or halogen when Y denotes $-CH_2-Ar$,

or a salt thereof.

2. A compound as claimed in claim 1, characterized by the formula 1a



(1a)

in which

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy- 1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino1-4C-alkylcarbonyl, hydroxy-2-4C-alkyl, fluoro-2-4C-alkyl,

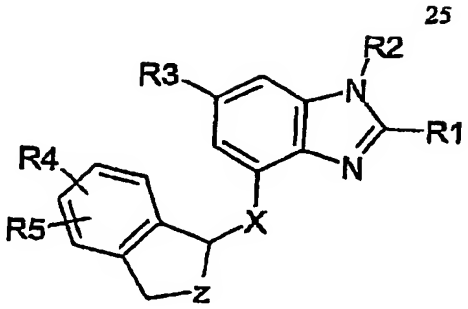
R3 is fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

X is O (oxygen) or NH and

Ar is a mono- or bicyclic aromatic residue, substituted by R4, R5, R6 and R7, which is selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2.3-triazolyl, indolyl, benzimidazolyl, furyl, benzofuryl, thienyl, benzothienyl, thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, chinolinyl and isochinolinyl,
where
R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,
R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,
R6 is hydrogen, 1-4C-alkyl or halogen and
R7 is hydrogen, 1-4C-alkyl or halogen.
and wherein
aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

or a salt thereof.

3. A compound as claimed in claim 1, characterized by the formula 1b



(1b)

In which

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy- 1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, aryl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, mono- or di-1-4C-alkylamino1-4C-alkylcarbonyl, hydroxy-2-4C-alkyl, fluoro-2-4C-alkyl,

R3 is hydrogen, halogen, fluoro-1-4C-alkyl, carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, hydroxyl, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxy, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxy, aryl, aryl-1-4C-alkyl, aryl-oxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R5 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxy,

X is O (oxygen) or NH and

Z has the meaning –CHR8- or –CHR8-CHR9-
where
R8 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,
R9 is hydrogen, 1-7C-alkyl, 2-7C-alkenyl, hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-

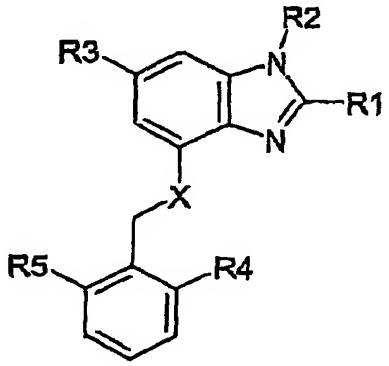
alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

and wherein

aryl is phenyl or substituted phenyl with one, two or three same or different substituents from the group of 1-4C-alkyl, 1-4C-alkoxy, carboxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxy and cyano,

or a salt thereof.

4. A compound of formula 1a as claimed in claim 2, characterized by the formula 1a-1



(1a-1)

where

R1 is hydrogen or 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, -CO-1-4C-alkoxy, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, or the group -CO-NR31R32,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl,

or where

R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

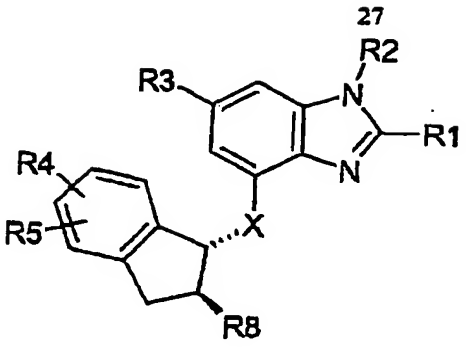
R4 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, trifluoromethyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

R5 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy and

X is O (oxygen) or NH

or a salt thereof.

5. A compound of formula 1b as claimed in claim 3, characterized by the formula 1b-1



(1b-1)

in which

R1 is 1-4C-alkyl,

R2 is hydrogen or 1-4C-alkyl,

R3 is carboxyl, -CO-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,
or where
R31 and R32 together, including the nitrogen atom to which both are bonded, are a pyrrolidino, piperidino, piperazino, N-1-4C-alkylpiperazino or morpholino group,

R4 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy or halogen,

R5 is hydrogen,

R8 is hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, hydroxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, halo-1-4C-alkoxy, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, mono- or di-1-4C-alkylamino-1-4C-alkylcarbonyloxy or 1-4C-alkoxy-1-4C-alkoxycarbonylamino,

X is O (oxygen) or NH,

or a salt thereof.

6. A compound of the formula 1a-1 as claimed in claim 4, in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3 is carboxyl, -CO-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl or the group -CO-NR31R32,
where
R31 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and
R32 is hydrogen or 1-4C-alkyl,

R4 is 1-4C-alkyl or 1-4C-alkylcarbonylamino,

R5 is 1-4C-alkyl,

X is O (oxygen) or NH,

or a salt thereof.

7. A medicament comprising a compound as claimed in claim 1 and/or a pharmacologically acceptable salt thereof together with customary pharmaceutical auxiliaries and/or excipients.

8. The use of a compound as claimed in claim 1 and its pharmacologically acceptable salts for the prevention and treatment of gastrointestinal disorders.

Abstract

The invention relates to 6-substituted benzimidazoles of formula 1, in which the substituents and symbols have the meanings indicated in the description. The compounds have gastric secretion inhibiting and excellent gastric and intestinal protective action properties.